pathological examination of a pleural tap specimen showed nothing abnormal. The pulmonary function test (fig 2) showed air trapping and a check-valve phenomenon. The total lung capacity was 6·65 l (normal 6·33 l) and residual volume 4·96 l (normal 2·09 l). The ventilatory capacity was 1·78 l (normal 4·24 l), forced expiratory volume in 1 s 0·32 l (normal 3·39 l), compliance 0·5 l/kPa (0·051 l/cm H_2O) (predicted value 2·6 l/kPa (0·26 l/cm H_2O), and diffusion capacity 20 μmol/sec/kPa (6 ml/min/mm Hg) (16% of predicted value).

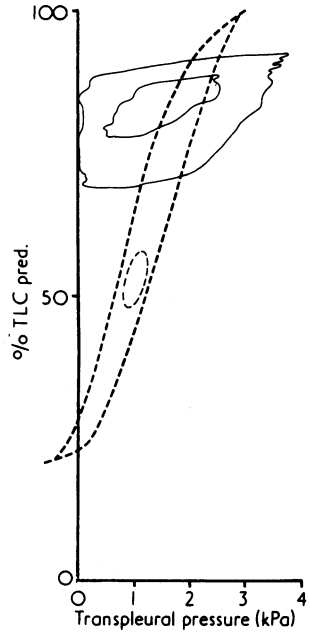

FIG 2—Pressure-volume curve (lung compliance) in patient (continuous line) compared with normal pressure-volume curve (interrupted line). Inner curves indicate tidal volume respiration; outer curves indicate maximal respiration.

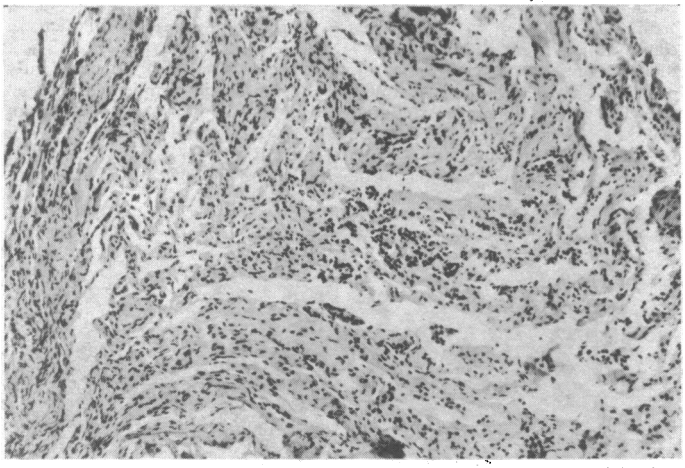

FIG 3—Representative areas of lung parenchyma showing fibrous thickening of alveolar walls. (H and E 98).

A lung scan with ^{67}Ga-citrate showed pathological accumulation in the right lower field. Lung tissue obtained from five different sites in the right lower lung by peripheral transbronchial biopsy via a flexible bronchoscope showed non-specific interstitial fibrosis (fig 3). No deposits of immunoglobulins or complement were present.

High-dose steroid treatment was considered, but the patient's condition rapidly deteriorated. She became feverish and increasingly dyspnoeic, started to cough, and produced large amounts of purulent sputum from which *Proteus mirabilis* and *Moraxella nonliquefaciens* were isolated. Her arterial blood gases (pH 7·34, Po_2 6·80 kPa (51 mm Hg), Pco_2 9·46 kPa (71 mm Hg), HCO_3 38 mmol/l) showed severe pulmonary insufficiency.

Before treatment with steroids could be started the patient died. Her sudden death was thought to be due to mucus plugging and subsequent hypoxia with arrhythmia. Permission to perform a necropsy was refused.

Comment

This 43-year-old woman died of rapidly progressive pulmonary insufficiency. The check-valve and air-trapping phenomena (remarkable findings in a patient who had never had pulmonary complaints) and the other pulmonary function values suggested a bronchiolitis with interstitial fibrosis,[8] which was confirmed by a lung biopsy. Various agents cause this condition: viral infections, various inhaled gases, medication, collagen diseases, sarcoidosis, immunological reactions and physical influences. In the absence of other agents we postulate a direct relation between the pulmonary fibrosis and her long-term use of practolol, which had already caused sclerosing peritonitis, keratitis superficialis, and pleural effusions. The first symptoms of bronchiolitis with interstitial fibrosis became evident six months after practolol treatment was discontinued. A latent subclinical period is often seen in drug-induced interstitial pulmonary reactions[8 9] as well as with the other adverse reactions attributed to practolol.[10] The precise mechanism remains unclear.

We thank Professor C A Wagenvoort for his evaluation of the biopsy specimens.

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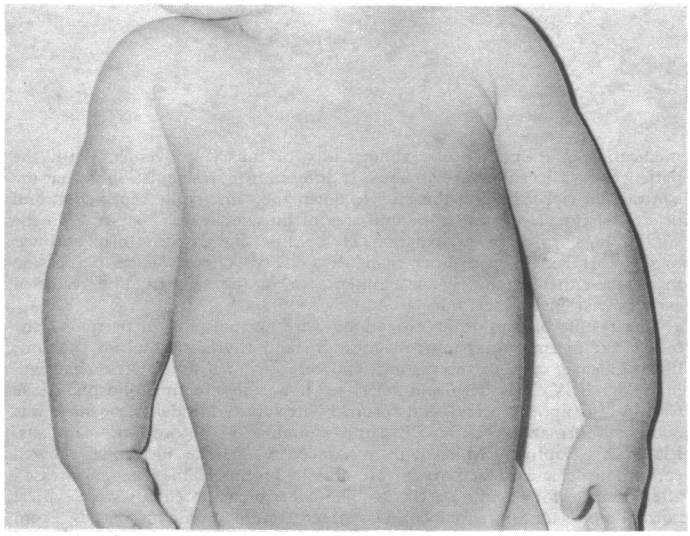
Hazards of intra-arterial diazepam

Diazepam is the drug of choice for status epilepticus.[1] Intravenous injection is needed for immediate effect, and in widespread use this has proved generally safe. Diazepam is also occasionally used to abolish seizures induced by spinal cord arteriography, and for this a local intra-arterial bolus of the drug before injection of the contrast material has been advised.[2] Despite evidence of the drug's safety when used intra-arterially in animals,[3] there have so far been two reported cases of accidental intra-arterial injection in children leading to extensive tissue necrosis and above-elbow amputation.[4 5] The two cases described below illustrate further these dangers.

Case 1

An 11-month-old boy was admitted in clonic status epilepticus. He was cyanosed and had a short respiratory arrest which responded to intermittent positive pressure ventilation (IPPV). He was obese and had poor peripheral vascular flow, and during an attempt to inject diazepam (Valium) into an antecubital vein 0·6 ml (3 mg) of diazepam was accidentally injected into the brachial artery. As the radial pulse remained palpable and there was no initial blanching of the arm distal to the injection, the needle was removed without any specific measures being taken.

Within half an hour, blotchy areas of pallor developed on the skin of the forearm, wrist, and palm of the hand and above the antecubital fossa. These areas of skin quickly became discoloured, and oedema of the forearm and palm of the hand developed. The fingers remained unaffected. Over the next 48 hours the swelling became tense (see figure), but fortunately the areas of localised skin damage did not progress to complete necrosis and sloughing, and the radial pulse always remained easily palpable with evidence of good distal blood flow to the fingers. Complete healing occurred within 14 days, and apart from limb elevation no specific measures such as anticoagulant or steroid treatment were used.



Case 1. Tense swelling of right forearm and palm.

Case 2

A full-term boy weighing 3340 g was delivered by spontaneous vertex delivery with an Apgar score of 8 at one minute and 10 at five minutes. Initially he was healthy but 38 hours after birth he was found to be apnoeic and cyanosed in his cot after a feed. After resuscitation with IPPV, oxygen, and external cardiac massage for bradycardia an umbilical venous catheter was passed and sodium bicarbonate 8·4% was infused. This failed to establish spontaneous respiration, so he was placed on a mechanical ventilator and an umbilical arterial catheter was inserted to allow blood gas monitoring. The umbilical venous catheter was removed. The umbilical arterial catheter was used for routine infusion of electrolyte solution over the next 16 hours, during which time sodium bicarbonate (8·4%) was infused slowly from time to time to correct the base deficit.

The infant developed generalised clonic seizures 41 hours after birth. To control these quickly 1 mg (0·2 ml) diazepam (Valium) followed by a further 0·5 mg (0·1 ml) was injected undiluted into the umbilical arterial catheter using a tuberculin-type syringe. The infusion of diazepam immediately produced generalised pallor of both legs, which lasted for five minutes. This improved slowly but his legs became oedematous and cyanosed, and these features persisted until the baby's death 13 hours later. His death was attributed to aspiration pneumonia on the basis of necropsy information. Histological examination of the abdominal aorta and the main arteries of the legs was not carried out.

Comment

Our two cases, together with those of Schneider *et al*[4] and Gabriele *et al*[5] show that diazepam, like thiopental sodium[6 7] and phenothazines[8] may produce severe vascular or end-organ damage when used intra-arterially even in small quantities. The drug has also occasionally produced thrombophlebitis when given by intravenous bolus.[9 10] These findings contradict those of Doppman *et al*,[3] who injected undiluted diazepam directly into the renal and mesenteric arteries of dogs and found no histological evidence of vascular or end-organ toxicity. They thus concluded that the drug was relatively safe in therapeutic doses when given intra-arterially and suggested that it could be used to prevent seizures induced by contrast media during carotid angiography.

The most commonly used commercial preparation, Valium, is relatively lipid soluble, being dissolved in propylene glycol, sodium benzoate, and alcohol. Diazepam and other lipid-soluble drugs were injected into the arteries of rabbits' ears by Knill and Evans,[11] who found that this resulted in progressive tissue swelling and oedema, which lead to eventual vascular occlusion and thrombosis. The solvents of parenteral diazepam were injected but produced no pathological lesion on their own. Studies suggested a direct membranolytic action of lipid-soluble drugs on vascular endothelium, which makes it doubtful whether any treatment, such as a local infusion of steroids or the use of anticoagulants, would be effective. This problem must, however, be kept in perspective, and the remote risks of intravenous injection—such as apnoea, bradycardia, and hypotension[12–14]—as well as vascular complications, should not outweigh the frequent and severe effects of prolonged status epilepticus.

Alternative routes of administration, such as the intramuscular or rectal routes, although safe, tend to prove ineffective in controlling status epilepticus immediately, as the drug takes up to 10 minutes to achieve a therapeutic level,[15] but there may be a place for rectal diazepam in the home or general practice, where intravenous injection is impractical.[15] In carotid and spinal angiography, however, the use of direct intra-arterial diazepam, and claims for its safety, should be questioned. With the increasing use of umbilical artery catheters in neonatal intensive care units for routine monitoring and feeding, the dangers associated with bolus injections of diazepam and other lipid-soluble drugs should also be appreciated.

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